

REMARKS

Applicants respectfully request reconsideration and further examination in view of the following remarks.

Claims 33-43, 45, 52-55, 69-85, 88-93, 96-101, and 104-141 are pending in this application. Claims 33, 38, 42, 43, 45, and 52 have been amended to recite that the soluble mutant flt3-L polypeptide "exhibits increased biological activity relative to full length wild type (SEQ ID NO:1) or mature human wild type (SEQ ID NO:18) flt3-L polypeptide." Support for this amendment can be found throughout the specification, including, for example, at page 10 and in the originally filed claims. This new recitation parallels the language of claim 1 of U.S. Patent No. 6,291,661, which issued from the application to which the present application claims priority. That issued claim recites that the mutant flt3-L polypeptide has increased or decreased biological activity relative to the full length or mature human flt3-L.

Method claims 42, 43, and 45 have also been amended to recite the particular disorders being treated. Claims 42, 43, and 45 are directed to methods of treating infection, myelodysplasia, and cancer, respectively. Support for these claims can be found throughout the specification, including, for example, at pages 13, 43, and 44. Claim 52 was amended and recites a method of augmenting an immune response "to an antigen." Claims 53, 54, and 55 were also amended to specify that the antigen is a bacterial vaccine antigen, a viral vaccine antigen, and a cancer vaccine antigen, respectively. Support for these amendments to claims 52-55 can be found throughout the specification, including, for example, at pages 4, 14, 38, and 43.

Claims 69, 75, 81, 89, 97, and 105 have been amended to recite that a basic amino acid “within amino acid positions 8-15 or 81-87” of the mature flt3-L polypeptide has been replaced with “a non-basic” amino acid or that “an amino acid within amino acid positions 116-124 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18) has been replaced with a basic amino acid.” Claims 70, 76, 82, 90, 98, and 106 have been amended to recite that the basic amino acid “replaced within amino acid positions 8-15 or 81-87 is the His at position 8 or” the Lys at position 84 of the mature human flt3-L. Support for these amendments to claims 69, 70, 75, 76, 81, 82, 89, 90, 97, 98, 105, and 106 can be found throughout the specification, including, for example at pages 7-8, 20, 65, 73, and 74.

Claims 111-141 have been added. Claims 111-132 are directed to methods for transplanting hematopoietic stem cells and/or progenitor cells. Support for these claims can be found through out the specification, including, for example, as set forth in the following chart.

Claim	Support in Specification
111 and 122	Pages 4-5, 12, 35-43
112 and 123	Pages 4 and 36
113 and 124	Page 36
114 and 125	Page 36
115-117 and 126-128	Pages 7-8, 20, 65, 73, and 74
118 and 129	Page 9
119 and 130	Pages 7, 59

120 and 131	Pages 57, 65
121 and 132	Page 23

New claim 133 depends from claim 45 (method of treating cancer) and further recites administering radiation or chemotherapy or both. Support for claim 133 can be found throughout the specification, including, for example, at pages 4 and 37.

Claims 134-139 depend from earlier claims and recite that “the amino acid replaced within amino acid positions 116-124 is the Trp at position 118 or the Gln at position 122 of the mature human wild type flt3-L (SEQ ID NO:18).” Support for this amendment can be found throughout the specification, including, for example, at pages 65 and 74.

Claim 140 is directed to a method of using the L27P flt3-L mutant for treating leukemia. Claim 141 depends from claim 140 and recites that the leukemia is acute myelogenous leukemia. Support for these claims can be found throughout the specification, including, for example, at pages 19-21 and 71-73.

This Amendment does not introduce any new matter.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 74, 80, 88, 96, 104, and 110 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. (Paper No. 10, p. 2.) The Office asserted that the claims are indefinite because the claims require

a protein comprising a given sequence and at the same time differing from that same sequence.

Although, applicants respectfully disagree, in an effort to expedite prosecution, claims 74, 80, 88, 96, 104, and 110 have been amended by deleting the phrase “and wherein said mutant flt3-L polypeptide comprises a substitution at one or more residues corresponding to amino acid positions 8-15, 81-87, or 116-124 of the mature human wild type flt3-L polypeptide (SEQ ID NO:18).” This amendment does not narrow the scope of the claims but merely claims the invention more clearly. Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 33-45, 52-55, and 69-110 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. (Paper No. 10, p. 3.) Applicants respectfully traverse this rejection.

The relevant inquiry for enablement is whether one reasonably skilled in the art could make and/or use the invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. M.P.E.P. § 2164.01. Factors to be considered when determining whether experimentation is undue include but are not limited to:

- (a) The breadth of the claims;
- (b) The nature of the invention;
- (c) The state of the prior art;
- (d) The level of one of ordinary skill;

- (e) The level of predictability in the art;
- (f) The amount of direction provided by the inventor;
- (g) The existence of working examples; and
- (h) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. at § 2164.01(a).

The Office begins its analysis by examining the breadth of the claims. The Office notes that “no specific activity (increase or decreased relative to wild-type, or totally inactive) is required by the claims.” (Paper No. 10, p. 3.) Applicants, however, have amended claims 33, 38, 42, 43, 45, 52 to recite that “the mutant flt3-L polypeptide exhibits increased biological activity relative to full length wild type (SEQ ID NO:1 or mature human wild type flt3-L polypeptide (SEQ ID NO:18).” Accordingly, the claims do require that the mutant flt3-L polypeptides have increased activity relative to wild-type flt3-L.

The Office acknowledges that the specification enables the use of certain specific mutants having increased activity, i.e., L-3H, H8Y, K84E, K84T, W118R, and Q122R, as well as multiple mutants K84E/Q122R and L-3H/H8Y/K84E/Q122R. (Paper No. 10, pp. 10-11.) But the Office also asserts that the “enablement is not commensurate with the broad scope of the claims.” (*Id.* at 11.) As noted above, the claims have been amended to recite that the mutant flt3-L polypeptides have increased activity. In addition, independent claims also 33, 38, 42, 43, 45, 52 also recite that the mutant polypeptides have one or more substitutions at position 24 of the full length human flt3-L or positions 8-15, 81-87, or 116-124 of the mature human flt3-L.

Applicants have given extensive direction and guidance in the specification for making and using polypeptides that are commensurate in scope with the pending claims. As explained in the specification, applicants identified “three linear clusters of high frequency amino acid substitution.”¹ (Specification, p. 59.) These mutational “hot spots” appear at positions 8-15, 81-87, and 116-124 of the mature human wild type flt3-L polypeptide, as recited in claims 33, 38, 42, 43, 45, and 52. Within these hot spots, applicants identified numerous mutants having increased activity relative to the full length human flt3-L polypeptide, including H8Y, K84E, K84T, W118R, and Q122R. (Specification, Table 1, p. 57.)

Having identified these “hot spots,” applicants also constructed several mutant flt3-L polypeptides containing one or more substitutions and having increased activity relative to the full length human wild type flt3-L polypeptide. (Specification, Example 5, pp. 68-70.) Applicants constructed these mutants by subcloning gene fragments into expression vectors and by PCR mutagenesis—techniques that were well known to a person skilled in the art at the time the application was filed.

To the extent the Office takes the position that the specification only enables those species that have been disclosed, it is well settled, even in the unpredictable arts, that section 112, first paragraph, does not require disclosure of every species

¹ Applicants identified an additional amino acid substitution at position -3 of the mature human flt3-L (i.e., at position 24 of the full-length human flt3-L) that gives rise to a mutant flt3-L having increased activity. (Specification, p. 7; Table 1, p. 57.) The L-3H mutant corresponds to L1H (SEQ ID NO:10) in the pending claims. Position 1 of SEQ ID NO:10 corresponds to position -3 of the mature human flt3-L polypeptide, or position 24 of the full-length human flt3-L polypeptide. (See Specification, p. 55.)

encompassed by the claims. See *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). As observed by the court in *Angstadt*:

To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples[.] More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed.

Id.

Accordingly, the relevant inquiry for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The test for undue experimentation does not depend on the amount of experimentation, since a considerable amount is permissible as long as it is routine. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); see also, M.P.E.P. § 2164.06.

Applicants are not trying to claim every possible mutant flt3-L polypeptide. The claims are directed to mutant flt3-L polypeptides having substitutions at specific amino acid positions or within specific amino acid regions that applicants have identified. It remains uncontroverted that the specification fully enables one of skill in the art to make substitutions at these residues. The question then becomes whether given applicants' teaching of the previously unknown importance of these residues, it would take undue

experimentation merely to test such mutants for their biological activity relative to wild-type flt3-L. Applicants submit that such testing is not undue.

Applicants' disclosure provides considerable direction and guidance on how to practice their invention. In the present application, applicants have identified three mutational hot spots in the mature human wild type flt3-L polypeptide, as well as specific substitutions of interest that occur at positions outside of these hot spots. In addition, applicants described how to generate mutant flt3-L polypeptides using known mutagenesis techniques. (Specification, pp. 48-50 and 68-69.) Next, applicants explained how to use routine screening assays to determine if the mutated flt3-L polypeptides bind to the wild type flt3 receptor. (Specification, pp. 50-52.) Mutant flt3-L polypeptides that bind to the wild type flt3 receptor can be further analyzed to determine if they have the desired biological activity. As explained in the specification, biological activity can be measured using the murine WWF7 cell assay according to previously published protocols. (Specification, p. 54.) Applicants also provided working examples (Examples 1-5), and identified numerous mutants having increased activity relative to the full length human flt3-L polypeptide, including L-3H, H8Y, K84E, K84T, W118R, Q122R, K84E/Q122R, and L-3H/H8Y/K84E/Q122R.. (Specification, Table 1, pp. 56-57 and 68-70.)

In addition, there was obviously a high level of skill in the art when the application was filed. Therefore, given 1) applicants' identification of specific areas of interest within the flt3-L polypeptide; 2) the scope of the pending claims, which are directed to methods of using mutant flt3-L polypeptides having substitutions within the areas of interest identified by applicants; 3) the high level of skill in the art; 4) the presence of

working examples in the specification; and 5) applicants' teaching of how to obtain and characterize the claimed mutant polypeptides using routine techniques, it would not require undue experimentation to practice the claimed invention.

The Office asserts that the claimed invention is unpredictable because even knowing the effect of a substitution at one position, one cannot predict the effect of a different substitution at the same position. (Paper No. 10, p. 4.) Even if the effect of a substitution cannot be predicted with certainty, however, applicants have taught one of skill in the art how to determine whether a particular substitution or mutation generates a mutant polypeptide that falls within the scope of the claims. Furthermore, applicants have directed the skilled artisan to specific regions of interest in the flt3-L polypeptide. While applicants acknowledge that some screening might have to be performed to identify additional mutant polypeptides within these regions of interest, applicants note that the test for undue experimentation does not depend on the amount of screening, since a considerable amount of screening is permissible as long as it is routine, or if the specification provides a reasonable amount of guidance regarding how the experimentation should proceed. (M.P.E.P. § 2164.06 and cases cited therein.) The methods used in the specification for generating mutant flt3-L polypeptides and screening them to identify mutant polypeptides with the unexpected biological activity were routine and well known in the art when the application was filed. Therefore, it would not require undue experimentation to generate mutant flt3-L polypeptides and screen them using the routine and well-known methods described in the specification to produce the mutant polypeptides recited in the claims.

For these reasons, applicants respectfully submit that the specification provides an enabling disclosure that is commensurate in scope with the claimed subject matter. Accordingly, applicants request withdrawal of this 35 U.S.C. 112, first paragraph, rejection.

CONCLUSION

In view of the foregoing remarks, applicants respectfully request the examination on the merits of this application and the timely allowance of the pending claims.

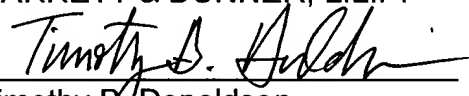
Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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